REMARKS

Claims 1-38 are pending in the application. Claims 3-13 and 33-37 have been previously withdrawn. Claims 16, 19, 20, 22, 24-26 has been cancelled without prejudice. Applicants respectfully submit that claims 1 and 38 have been amended to recite the subject matter claimed in cancelled claim 19.

New claims

New claims 39-42 have been added to specifically protect various specific sequences and commercial embodiments. Support can be found on pages Example 5 and Figs. 25, 26, 29, 30, and 35. No new matter has been introduced. These claims should not raise any new grounds for rejection nor require a new search. It is respectfully requested that these claims be accepted and entered.

Claim rejections - 35 U.S.C. § 103(a)

The Examiner maintains her rejection of claim 16 under 35 U.S.C. 103(a) as being obvious in view of Peyman *et al.*

Further, claims 1, 2, 14-15, 17-32 and 38 have been rejected under 35 U.S.C. 103(a) as being obvious in view of Peyman *et al.*

The Examiner mentions that our arguments submitted September 28, 2006 regarding the fact that Peyman *et al.* only teaches that the efficacy of the tested oligonucleotides is dependent on the presence of 10 guanines extension at each extremity of the oligonucleotide, were not convincing. The Examiner alleges that this argument relates to the G-quartet structures, which are not mentioned in the claims. Furthermore, the Examiner alleges that Peyman *et al.* teaches that the oligonucleotide activity can be improved by extending the oligonucleotides at the 3' and/or 5' end by from one to ten guanines. In addition, Peyman teaches that the oligonucleotides, from 10 to 40 nucleotides in length, are used to treat disease caused by a virus. The Examiner further mentions that Peyman teaches sense nucleotides as well as antisense. Therefore, the teaching found in Peyman renders obvious the claimed invention.

Regarding rejection of claims 1, 2, 14-15, 17-32 and 38, the Examiner mentions that it would have been *prima facie* obvious to a person skilled in the art at the time the invention was made to use the oligonucleotides to treat RSV or parainfluenza because the composition has been shown to be effective against viral infections. A person skilled in the art would have been motivated to use the pharmaceutical composition because Peyman has demonstrated that it is effective against diseases caused by viruses, and reasonably would have expected success because of the teachings of Peyman *et al.*.

In order to overcome this rejection, Applicants first point out that claims 16, 19, 20, 22, 24-26 have been cancelled. Secondly, it is respectfully submitted that nowhere is it taught or even suggested in Peyman *et al.* that oligonucleotides have antiviral activity against multiple viruses acting by a non-sequence complementary mode of action. Moreover, Peyman *et al.* is only enabled for four antisense oligonucleotides against HSV-1 in cell culture (as disclosed in column 14, lines 14-19 in Peyman). Peyman *et al.* only teaches how to stabilize and improve cell penetration by capping oligonucleotides (with the addition of a cap of guanine at their extremities). When considering the sequences disclosed by Peyman *et al.*, all of the sequences disclosed therein are antisenses. Moreover, Peyman *et al.*, in column 6, lines 8-9, teaches that the effective oligonucleotides are understood to mean antisense oligonucleotides. By definition, an "antisense" is a molecule that interacts with complementary strands of nucleic acids, modifying the expression of genes. Consequently, a person skilled in the art would recognize that an antisense RNA or single-stranded antisense DNA is a molecule which is complementary to the nucleic acid sequence of a gene of interest. Thus, the mechanism of action of an antisense is sequence dependent since it must be complementary to a strand of nucleic acids in order to interact and modify the expression of the gene of interest. In addition, such person skilled in the art would conclude that SEQ ID NOs: 1-34 in Peyman *et al.* represent sequences that are complementary to a known gene, and thus represent possible antisense oligonucleotides. The following Table identifies the gene targeted by these antisenses:

Patent Seq ID	Sequence	Homologous to (% coverage)	Accession #
1	ACACCCAATTCTGAAAATGG	HIV-1, complete genome (100)	AF003819.3
2	AGGTCCCTGTTCGGGCGCCA	HIV-1 proviral DNA, complete genome (100)	AB289588.1
3	GTCGACACCCAATTCTGAAAATGGATAA	HIV-1, complete genome (100)	AF003819.3

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Patent Seq ID	Sequence	Homologous to (% coverage)	Accession #
4	GCTATGTCGACACCCAATTCTGAAA	HIV-1 proviral DNA, complete genome (100)	AB287367.1
5	GTCGCTGTCTCCGCTTCTTCTTCCTG	HIV-1 isolate B055AA from USA tat protein (tat) gene, partial cds (100 [bases 1-22])	AY734162.1
6	GTCTCCGCTTCTTCTTCCTGCCATAGG	HIV-1 proviral DNA, complete genome (100 [bases 10-27])	AB289588.1
7	GCGGGGCTCCATGGGGGTCG	Human herpesvirus 1 complete genome (100)	X14112.1
8	CAGCTGCAACCCAGC	Homo sapiens angiomotin like 1 (AMOTL1), mRNA (100)	NM_130847.2
9	GGCTGCTGGAGCGGGGCACAC	Homo sapiens MYC gene for c-myc proto-oncogene and ORF1 (100)	X00364.2
10	AACGTTGAGGGGCAT	Homo sapiens v-myc myelocytomatosis viral oncogene homolog (100)	NM_002467.3
11	GTGCCGGGGTCTTCGGGC	Homo sapiens mRNA for v-myb myeloblastosis viral oncogene (100)	AJ616235.1
12	GGAGAACATCATGGTCGAAAG	Mouse c-fos oncogene (100)	V00727.1
13	CCCGAGAACATCATGGTCGAAG	Mouse c-fos oncogene (100)	V00727.1
14	GGGGAAAGCCCGGCAAGGGG	Mouse c-fos oncogene (100)	V00727.1
15	CACCCGCCTTGGCCTCCCAC	Multiple human genomic hits (100)	
16	GGGACTCCGGCGCAGCGC	Human mRNA for precursor of epidermal growth factor receptor (100)	X00588.1
17	GGCAAACTTTCTTTTCCTCC	Homo sapiens epidermal growth factor receptor (100)	NM_201284.1
18	GGGAAGGAGGAGGATGAGG	Mus musculus mRNA for p53, complete cds (100)	AB020317.1
19	GGCAGTCATCCAGCTTCGGAG	Mouse mRNA for transformation associated protein p53 (100)	X00741.1
20	GCAGTAAGCATCCATATC	Felis catus integrin beta 1 (100)	NM_001048160.1
21	CCCCCACCACTTCCCCTCTC	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
22	CTCCCCCACCACTTCCCCTC	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
23	GCTGGGAGCCATAGCGAGG	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
24	ACTGCTGCCTCTTGTCTCAGG	Homo sapiens HES2 gene (100 [bases 2-16] and multiple genomic hits (100)	NM_019089.3
25	CAATCAATGACTTCAAGAGTTC	Homo sapiens selectin E (endothelial adhesion molecule 1) [bases 7-22] and multiple genomic hits (100)	NM_000450.1
26	GGTCCCTGTTCGGGCGCCA	HIV-1 proviral DNA, complete genome (100)	AB289588.1
27	GTGCCGGGGTCTTCGGG	Homo sapiens mRNA for v-myb myeloblastosis viral oncogene (100)	AJ616235.1
28	GGAGGATGCTGAGGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
29	GGAGGATGCTGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
30	CAGGAGGATGCTGAGGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
31	GGCTGCCATGGTCCC	Homo sapiens fibroblast growth factor 2 (100)	NM_002006.3
32	TCATGGTGTCCTTTGCAGCC	Homo sapiens procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (100 [bases 1-15] and multiple genomic hits (100)	NM_001084.4
33	TCATGGTGTCCTTTGCAG	Homo sapiens procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (100 [bases 1-15] and multiple genomic hits (100)	NM_001084.4
34	AAGTTCATGGTTTCGG	Homo sapiens vascular endothelial growth factor A (100)	NM_003376.4

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In column 6, lines 30-31; column 8, lines 29-30; column 10, lines 35-36; column 11, lines 4-5; and column 14, lines 14-19 of Peyman *et al.*, it is clearly stated that the following oligonucleotides are examples of a novel antisense effective against the following targets:

SEQ ID NOs	Target gene
35-46	HIV
47-54	HSV-1
55-56	c-Ha-ras
57-60	c-myc
61-63	c-myb
64-70	c-fos
71-72	p120
73-77	EGF receptor
78-81	p53 tumor suppressor
82-83	bFGF
84	VEGF
85-86	VLA-4
87-94	ICAM
95-98	ELAM-1
99-103	TNF-alpha
104-105	HSV-1

Consequently, SEQ ID NOs: 1-105 all represent antisense oligonucleotides which are complementary to a portion of the nucleic acid sequence of a specific gene. Thus, by its inherent properties, as well as by definition, an antisense will modify the expression of a gene by a sequence dependent and complementary mode of action. The present application teaches oligonucleotides having a non-sequence complementary mode of action. For example, with randomer oligonucleotides, as taught in the present description, due to the nature of the preparation used to produce them, a sequence complementary mode of action cannot occur. On page 34 of the present description, it is clearly disclosed that for a randomer oligonucleotide of 40 bases in length, any particular sequence in the population would theoretically represent only $1/4^{40}$ or $8.27X10^{-25}$ of the total fraction. Given that 1 mole = $6.022X10^{23}$ molecules, and the fact that the largest synthesis is currently done on a 15 micromole scale, all possible sequences will not be present. Also, there is most probably only one copy of each sequence. Consequently, by its inherent properties, the mode of action of these oligonucleotides is sequence independent and does not require complementarity to the nucleic acid sequence of a gene.

In addition, it is clearly stated in Peyman *et al.* (column 1 and 2, under the Summary section), that:

> "*It has now been found that a very simple option exists for significantly improving unmodified or modified oligonucleotides with regards to their nuclease resistance and cell penetration, so that their activity is substantially improved, by extending the oligonucleotides at the 3' end and/or 5' end by from one to 10 guanines.*
>
> *Surprisingly, the novel oligonucleotide also exhibit a tendency to associate or aggregate. It is possible that they too form G quartet structures by the association of two or more oligonucleotide. Such structures would protect against exonuclease degradation and lead to an increased uptake in cell.*"

Thus, Peyman *et al.* discloses and claims antisenses which are complementary to a target sequence and which have a Cap of guanine(s) at its 5' and/or 3' extremity to simply increase nuclease resistance and cell penetration. Nowhere in the present application is it taught, claimed or required that the oligonucleotides of the present invention need to possess a Cap of guanines in order to increase its nuclease resistance and cell penetration, or that they be antisense or have sequence complementarity to a target so that their activity will be improved. Again, a person skilled in the art would recognize that Peyman *et al.* teaches antisense oligonucleotides wherein the stabilized antiviral activity depends on the presence of a Cap of guanines. Thus, the stabilization of the antisenses disclosed in Peyman is dependent on the presence of a secondary structure since, as stated in Peyman *et al.* (see column 1, lines 55-57), oligonucleotides which contain short segments of G residues are able to form intramolecular structures called G-quartets. Thus, not only is the antiviral activity dependent on the sequence, but the stabilization of the antisenses disclosed in Peyman is dependent on complementarity (in order to form the G-quartet structure).

In view of the arguments presented hereinabove, it is believed that claims 1, 2, 14, 15, 17, 18, 21, 23, 27-32 and 38 now on file are novel and inventive in view of the teaching of Peyman *et al.*, and thus reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

It is submitted, therefore, that the claims are now in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 1, 2, 14, 15, 17, 18, 21, 23, 27-32 and 38-42 at an early date is solicited.

No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application can be expedited.

Respectfully,

Date: May 24, 2007

By: ______________________

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Enc. Petition for extension of time